The Egyptian clinical practice guidelines for the diagnosis and management of metabolic associated fatty liver disease

Yasser Fouad, Gamal Esmat[1], Reda Elwakil[2], Serag Zakaria[1], Ayman Yosry[1], Imam Waked[3], Maissa El-Razky[1], Wahid Doss[1], Magdy El-Serafy[1], Ebraheem Mostafa[4], Mahmood Anees[5], Mohamed A. Sakr[2], Nadia AbdelAty[2], Ashraf Omar[1], Samy Zaki[7], Amgad Al-zahaby[7], Hamdy Mahfouz[8], Maysaa Abdalla[9], Mahmoud Albendary[10], Abdel-Khalek Hamed[11], Ahmed Gomaa[12], Adel Hasan[13], Sherif Abdel-baky[6], Medhat El sahhar[14], Gamal Shiha[15], Dina Attia[16]

Writing team of the Egyptian MAFLD Research Group (EMRG):
Ebada Saeed[17], Enas Kamal, Shamardan Bazeed[18], Mai Mehrez[19], Shereen Abdelaleem[1], Yasmine Gaber[1], Mohammed Abdallah[20], Asmaa Salama[16], Doaa A. Tawab[21], Shaymaa Nafady[16]

Department of Gastroenterology, Hepatology and Endemic Medicine, Faculty of Medicine, Minia University, [1]Department of Endemic Medicine and Hepatology, Faculty of Medicine, Cairo University, Cairo, [2]Tropical Medicine Department, Faculty of Medicine, Ain Shams University, [3]Department of Hepatology and Gastroenterology, National Liver Institute, Menoufia University, Shebeen El Kom, [4]Theodore Bilharz Research institute, Cairo, [5]Department of Gastroenterology and Hepatology, [6]Gastroenterology, Hepatology and Endemic Medicine, Faculty of Medicine, Tanta University, Tanta, [7]Department of Hepatogastroenterology and Infectious Diseases, Al-Azhar University, Cairo, [8]Department of Hepatogastroenterology and Infectious Diseases, Al-Azhar University, Assuit, [9]Department of Gastroenterology, Hepatology and Endemic Medicine, Faculty of Medicine, Zagazig University, Zagazig, [10]Department of Gastroenterology, Hepatology and Endemic Medicine, Faculty of Medicine, Mansura University, Mansura, [11]Department of Internal Medicine, Hepatology, and Diabetes, Egyptian Military Medical Academy, Cairo, [12]Department of Gastroenterology, Hepatology and Endemic Medicine, Faculty of Medicine, Fayoum University, Fayoum, [13]Department of Gastroenterology, Hepatology and Endemic Medicine, Faculty of Medicine, Suez Canal University, Suez, [14]Egyptian Association for the Study of Liver and Gastrointestinal Disease (EASLGD), Police Medical Academy, Cairo, [15]Hepatology and Gastroenterology Unit, Internal Medicine Department, Faculty of Medicine, Mansoura University, Mansoura, [16]Department of Gastroenterology, Hepatology and Infectious Diseases, Faculty of Medicine, Beni-Suef University, Beni Suef, [17]Department of Gastroenterology, Hepatology and Infectious Diseases, Faculty of Medicine, Benha University, Benha, [18]Department of Tropical Medicine and Gastroenterology, Faculty of Medicine, South Valley University, Qena, [19]Department of Hepatology, NTHMRI, Cairo, [20]Department of Medical Research Division Medicine, National Research Centre, Giza, [21]Department of Tropical Medicine and Gastroenterology, Faculty of Medicine, Assuit University, Assuit, Egypt

Abstract

The landscape of chronic liver disease in Egypt has drastically changed over the past few decades. The prevalence of metabolic-associated fatty liver disease (MAFLD) has risen to alarming levels. Despite the magnitude of the problem, no regional guidelines have been developed to tackle this disease. This document provides the clinical practice guidelines of the key Egyptian opinion leaders on MAFLD screening, diagnosis, and management, and covers various aspects in the management of MAFLD. The document considers our

Address for correspondence: Dr. Yasser Fouad, Professor of Gastroenterology, Hepatology and Infectious Diseases, Faculty of Medicine, Minia University, Minia 61519, Egypt.
E-mail: Yasser.abdallah@mu.edu.eg
Submitted: 01-Jul-2021 **Revised:** 24-Oct-21 **Accepted:** 31-Oct-2021 **Published:** 25-Jan-2022

Access this article online

Quick Response Code:

Website: www.saudijgastro.com

DOI: 10.4103/sjg.sjg_357_21

How to cite this article: Fouad Y, Esmat G, Elwakil R, Zakaria S, Yosry A, Waked I, *et al*. The Egyptian clinical practice guidelines for the diagnosis and management of metabolic associated fatty liver disease. Saudi J Gastroenterol 2022;28:3-20.

local situations and the burden of clinical management for the healthcare sector and is proposed for daily clinical practical use. Particular reference to special groups was done whenever necessary.

Keywords: Egyptian, guidelines, MAFLD

INTRODUCTION

The landscape of chronic liver disease in Egypt has drastically changed over the past few decades, with the decreasing prevalence of viral hepatitis and increasing prevalence of metabolic-associated fatty liver disease (MAFLD) (formerly known as nonalcoholic fatty liver disease [NAFLD]). MAFLD has risen in prevalence to alarming levels, placing an enormous burden on individuals and healthcare systems. Despite the magnitude of the problem, no regional guidelines have been developed to tackle this disease.

This document provides the clinical practice guidelines of the key Egyptian opinion leaders on MAFLD screening, diagnosis, and management. The participants performed a detailed systematic review of the literature retrieved after an extensive PubMed search up to March 2021 on particular domains of interest, and deciphered the current scientific evidence into simple practice guidelines with recommendations to improve the routine clinical practice on patients with MAFLD.

These guidelines cover various aspects in the management of MAFLD, including epidemiology, screening, diagnosis, evaluation, and treatment. The statements in this guideline are according to the Grading of Recommendation Assessment, Development, and Evaluation approach.[1] In case of disagreement, the final grading of evidence and recommendations was determined by a majority vote.

The document considers our local situations and the burden of clinical management for the healthcare sector and is proposed for daily clinical practical use and to orchestrate it with the advancing knowledge and research of MAFLD. Particular reference to special groups was done whenever necessary. The ultimate goal is to improve awareness of MAFLD and patient care, encourage dialogue between various stakeholders for the development of health policies, and assist in the decision-making process by providing evidence-based data. In addition, we identified some areas of gap in our knowledge and set an agenda for calling for research studies in our Egyptian population. As it is expected that new evidence will emerge from Egyptian cohorts, updates to these guidelines might be required in the future.

EPIDEMIOLOGY

Over the past five decades, the nutrition pattern of the Egyptian population has witnessed an overall increase in energy intake. Nutrition moved to a type of diet with increases in the intake of fast food, red meat, vegetable oils, processed foods, and soft drinks, and decrease in the intake of fresh fruits and vegetables.[2] It is estimated that up to 40% of the fat consumed by women in Egypt is saturated fat,[3] and the rates of the low intake (below five servings per day) of fresh fruit and vegetables in Egypt is up 80%.[4] In contrast, Egypt is on track to meet the World Health Organization (WHO) recommendations for the elimination of hepatitis C, with a dramatic decline in the number of hepatitis C virus (HCV) cases.[5,6] Therefore, the profile of liver disease in Egypt is witnessing a trajectory shift from one of communicable to noncommunicable diseases.[7-9]

Parallel to these changes, although the prevalence of overweight and obesity (a body-mass index (BMI) of 25 kg/m^{2}or greater) has risen globally between 1980 and 2013 in both men (from 28.8% to 36.9%) and women (from 29.8% to 38.0%); the largest increases in the rate of obesity worldwide were seen in Egypt.[10] Indeed, Egypt is among the top 10 countries with the highest levels of obesity worldwide; >71.2% of adult men were overweight and 26.4% were obese, and 79.4% of adult women were overweight and 48.4% were obese.[10] Worryingly, the prevalence rates of overweight and obesity among school children and adolescents were 31.5% and 12.7%, respectively, among boys less than 20 years, and 39.5% and 14.4%, respectively, among girls of the same age group.[11] Similarly, the average prevalence of insufficient physical activity in Egypt is 31.0%, which is higher than the global prevalence of 27.5%. This number was even higher in females (38.8%) than in males (23.2%).[10]

The prevalence of MAFLD has risen in parallel with the aforementioned changes, with direct clinical and economic burden. Although there is scant data on the magnitude of MAFLD in Egypt, available data suggest that Egypt has one of the highest prevalence of MAFLD, affecting more than one-third of the population, compared to a global prevalence of about 25%.[9,12,13] Specific studies suggest that the prevalence range of MAFLD in Egypt is approximately 47.5%, with 56.7% having fibrosis,[14] and it was present in

approximately 15.8% of children.[15] Another retrospective study of 2097 patients from large Egyptian tertiary care liver centers revealed that the leading cause of patient presentation is MAFLD (44.9%).[16]

Unfortunately, the awareness of patients and physicians in Egypt about the magnitude of the problem and its risks is not sufficient.[17,18] Therefore, it is not surprising that NAFLD is seriously underdiagnosed in real-world settings,[19,20] with most patients being diagnosed incidentally when cirrhosis has already developed.[21]

DEFINITION AND DIAGNOSIS OF MAFLD

According to the Middle East and North Africa consensus,[22] the Egyptian guidelines endorse the proposal of the international consensus panel for the redefinition of fatty liver disease[23-25] The diagnosis of MAFLD is based on the presence of liver steatosis (detected by liver histology, imaging, or noninvasive biomarkers), together with the presence of at least one of three criteria, which include (i) overweight or obesity, (ii) type 2 diabetes mellitus (T2DM), and (iii) clinical evidence of metabolic dysfunction. An avalanche of evidence supports the superiority of the new definition compared to the old NAFLD definition.[26-29] In addition, the simplicity of the criteria render it suitable for resource-constrained settings[22,27,29-32] [Figure 1].

NATURAL HISTORY OF MAFLD

Egypt had the highest global age-standardized death rate from cirrhosis in all the years from 1990 to 2017, which was 103.3 per 100,000, despite a 22.4% decrease from 1990.[33] This decrease is likely driven by the rapid decrease in the HCV death rate. The decline is expected to continue over the next 5 years. However, the actual burden of MAFLD in Egypt is not fully characterized. Alarming numbers are emerging. In 2017, 12.8% of deaths due to cirrhosis in Egypt were caused by MAFLD and 6.5% were caused by other causes, most likely from undiagnosed MAFLD.

In addition, the age-standardized prevalence rates of compensated and decompensated cirrhosis due to MAFLD per 100,000 increased from 312.3 and 19.4 in 1990 to 340 and 26 in 2017, respectively. Furthermore, the proportion of causes for disability-adjusted life years, a time-based measure that combines years of life lost due to premature mortality caused by MAFLD-related cirrhosis, in 2017 was 12%.[33]

MAFLD is currently progressively increasing as the main cause of hepatocellular carcinoma (HCC) globally.[34] The available data suggest that Egypt has one of the highest increases in the age-standardized incidence rate of MAFLD-related HCC globally, with an increase of 89.8% between 1990 and 2017.[35] Consistently, another study in Egypt showed that the annual proportions of MAFLD-related HCC increased significantly from 4.3% in 2010 to 20.6% in 2020, whereas HCV-related HCC declined from 94.8% to 76.7%.[36]

Compared to other liver diseases, a recent study showed that MAFLD-related HCC had a significantly higher percentage of death within 1 year of diagnosis and had approximately 5 months shorter survival time than HCC related to viral hepatitis (HCV/hepatitis B virus [HBV]).[37] Notably, a 2018 meta-analysis demonstrated that noncirrhotic patients with MAFLD had up to 261% increased risk of HCC compared to all other etiologies of liver disease.[38]

Similarly, MAFLD was found to be the most rapidly growing indication for liver transplantation in multiple countries in the region[39]; for example, more than 63% of referred patients for liver transplantation in Kuwait in 2018–2019 had MAFLD-related cirrhosis.[40] Though it would be expected that Egypt would have a similar trend, further studies are required to confirm this.

EXTRAHEPATIC MANIFESTATIONS OF MAFLD

MAFLD is a multisystem disease associated with a plethora of extrahepatic manifestations and comorbidities.[41]

MAFLD is associated with cardiovascular disease (CVD)[41] and chronic kidney disease (CKD)[42] risk. In addition to liver cancer, MAFLD is implicated in the risk of various extra-hepatic cancers.[43] CVD and malignancy represent the main causes of death in MAFLD patients,[44] while baseline liver fibrosis is the strongest predictor.[45,46] Therefore, physicians treating patients with MAFLD should be encouraged to evaluate and undertake risk factor and comorbidities management as part of a holistic approach to patient care.

CVD risk can be assessed using risk scores (e.g., atherosclerotic cardiovascular disease risk estimator). MAFLD patients with a history of a cardiovascular event or presenting with clinically active CVD or evidence of metabolic comorbidities and/or severe liver disease, should be referred for evaluation by a cardiologist for further evaluation. Otherwise, patients who are negative or assessed as having low CVD risk can be re-evaluated every 2–3 years.[47]

The types and choice of medications for treatment of T2DM, hypertension, and dyslipidemia are beyond the scope of these recommendations and should be followed according to the specific disease guidelines.

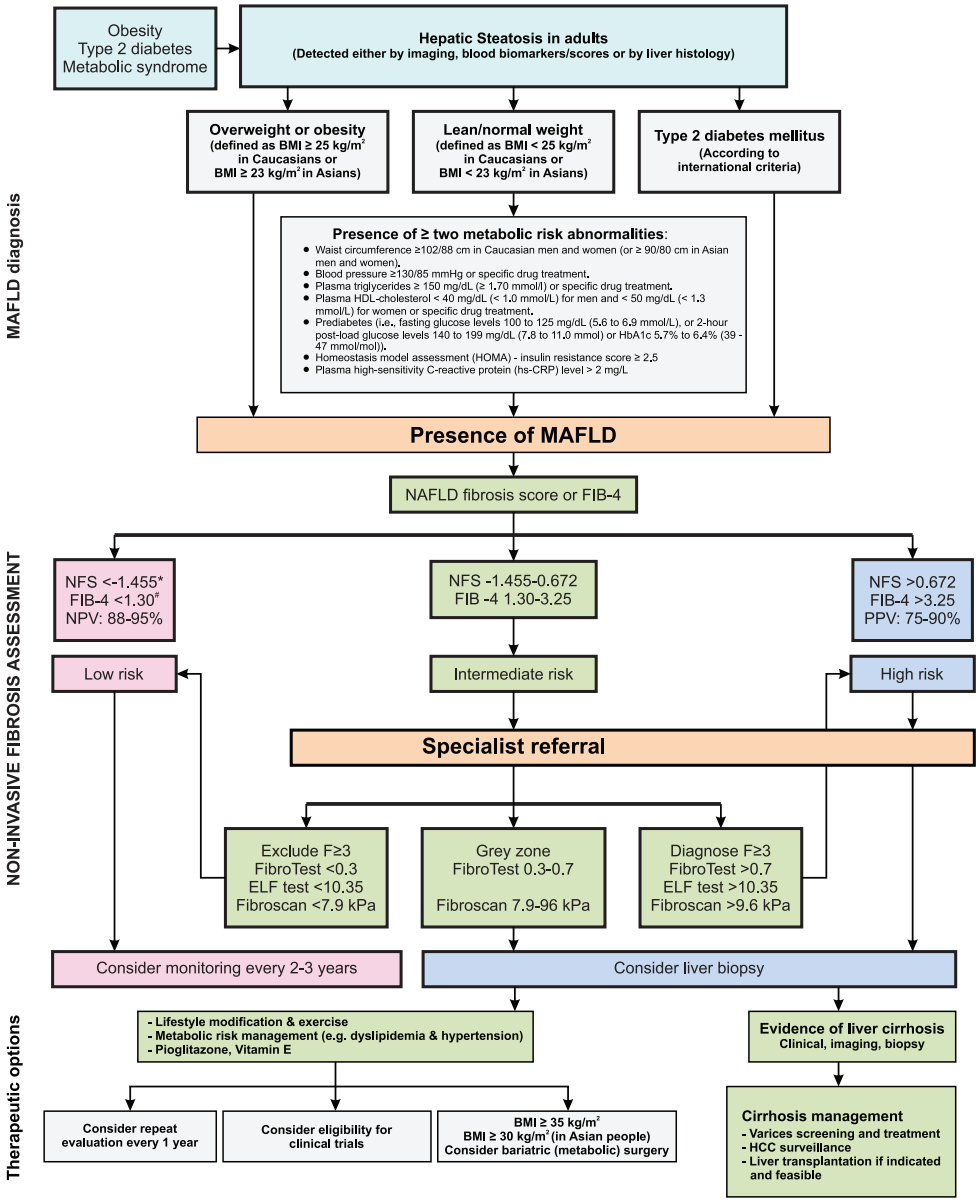

Figure 1: The Egyptian guidelines recommended an algorithm to diagnose MAFLD in suspected patients, and evaluation, management, and monitoring disease severity approach for confirmed subjects. The proposed model is a primary care-based multidisciplinary care model for MAFLD, whereas the initial identification of cases would mainly occur at primary care, with an attached appropriate referral pathway for specialist care, as illustrated.

Recommendations

- MAFLD patients should be evaluated for CVD and referred to a cardiologist, if needed (A1)
- Consideration of other extra-hepatic manifestations of MAFLD is recommended (B1).

SCREENING FOR MAFLD

Screening for MAFLD by ultrasonography is recommended in at-risk populations, including those with overweight/obesity, T2DM, or metabolic dysfunction. Patients with MAFLD should be evaluated for the presence of other metabolic comorbidities, such as T2DM, hypertension, and dyslipidemia and be treated appropriately.

Recommendations

- Screening for MAFLD by ultrasonography is recommended in at-risk populations, including those with T2DM or metabolic dysfunction (A1).
- Patients with MAFLD should be evaluated for the presence of other metabolic comorbidities, such as T2DM, hypertension, and dyslipidemia and be treated appropriately to reduce the risk of cardiovascular and kidney disease. (A1)

NONINVASIVE TESTS

Noninvasive modalities that could be used in clinical practice are needed for diagnosis of MAFLD, assessing disease severity, and monitoring disease progression and treatment response.[48]

In routine clinical practice, abdominal ultrasonography is commonly used and is usually sufficient for the detection of hepatic steatosis.[49] However, it has poor sensitivity for detecting mild levels of steatosis.

The controlled attenuation parameter (CAP) is more sensitive than ultrasonography and is being increasingly utilized to assess liver fat and can be obtained simultaneously with a liver stiffness measurement (LSM) by vibration-controlled transient elastography (VCTE) (FibroScan).[50] The optimal cut-off for identifying fatty liver by CAP was suggested by an earlier meta-analysis, to be 248 dB/m.[50] However, subsequent studies suggested higher optimal cut-off points, 288 dB/M[51] and 302 dB/M.[51] Further studies in Egyptian population are required. In addition, an interquartile range of >30–40 dB/m has been suggested to be associated with less reliable CAP measurements.[51,52] Probe selection also influences CAP values, and optimal cut points for the diagnosis of fatty liver are lower using the M probe versus the XL probe.[53]

MRI-based techniques such as MRI-PDFF and proton-magnetic resonance spectroscopy (MRI-MRS) can detect small amounts of liver fat and is considered the gold standard to quantify liver fat. Currently, the main indication for liver fat fraction measurement by MRI is for clinical trials.[54]

Numerous steatosis simple scores have been proposed as an alternative method for the assessment of hepatic steatosis, particularly in large-population studies. In particular, the FLI, which includes BMI, waist circumference, triglycerides, and GGT, is widely used[55] and has been recently validated in a large cohort of 35,335 patients with MAFLD.[56]

Simple fibrosis scores only involve clinical and routine laboratory parameters, are widely validated and reproducible scores, and are inexpensive; these include the aspartate aminotransferase (AST)-to-platelet ratio index (APRI),[57] Fibrosis-4 index (FIB-4),[58] and NAFLD fibrosis score (NFS).[59] Patients can be defined as being at low or high risk for advanced fibrosis for each score according to the following cut-offs: APRI (0.5 and 1.5), FIB-4 (1.30 and 2.67), NFS (<−1.455 and > 0.67611). These cut-offs need to be further validated in Egyptian cohorts. These scores are well suited for use as an initial assessment in primary-care or resource-poor settings.[60,61] Subjects with indeterminant results or high scores are to be referred to specialists for further evaluation to appropriately guide the management of patients.

Proprietary biomarkers of fibrosis include N-terminal type III collagen propeptide (Pro-C3). A Pro-C3 based algorithm, the ADAPT algorithm, that includes age, T2DM, and platelet count has shown high diagnostic accuracy for advanced fibrosis in tertiary hospitals[62] and general low-risk populations cohorts.[63]

Liver stiffness measurement (LSM) obtained through VCTE, which is commercially available as FibroScan, is increasingly used in Egypt. An M probe and XL probe are both available. The majority of MAFLD patients can achieve successful measurement with the XL probe.[64,65] The quality criteria to guide its use are a minimum of 10 measurements, of which more than 60% should be valid, and the ratio of the median valid LSM to IQR should not exceed 0.3. Magnetic resonance elastography has higher accuracy and success rates compared to VCTE, but its wider use is limited by availability and cost.[66,67] The combination of LSM and simple fibrosis scores has the advantage of increasing accuracy and decreasing the percentage of patients classified as a gray zone. In contrast, there has not been any robust biomarker for steatohepatitis.

Recommendations

- Noninvasive modalities that could be used in clinical practice are needed for diagnosis of MAFLD, assessing disease severity, and monitoring disease progression and treatment response (A1).
- Abdominal ultrasonography is the recommended first-line tool for the detection of hepatic steatosis (A1).
- Controlled attenuation parameter (CAP) measurement is a more sensitive tool than ultrasonography. Thus, if available, it can be used for both diagnosis and disease monitoring (B1).
- Although considered the gold standard to quantify liver fat, MRI-based techniques are not recommended for routine clinical practice (A1).
- The exclusion of high risk of significant fibrosis is acceptable using simple noninvasive biomarkers and scores of fibrosis (A2).
- The confirmation of significant fibrosis can be done by liver stiffness measurement by VCTE and/or sequential combination with serum biomarkers/scores (A2).
- As per the clinical judgment, liver biopsy could be required in some cases, particularly in patients with indeterminant (gray) range scores (B2).
- There is no strong biomarker for steatohepatitis, and liver biopsy remains the only diagnostic test of choice (A1).

LIVER BIOPSY

With the high prevalence of MAFLD, biopsy evaluation is indicated mainly to confirm the diagnosis when the clinical picture is atypical, to aid in the assessment of prognosis when some cases fall into the gray zone,[68] to identify additional causes of liver disease, and to determine if a patient might benefit from an intervention.

The use of a 16-G or wider needle via a percutaneous approach under ultrasound guidance is recommended for the biopsy. An adequate histology specimen should comprise at least 10 portal tracts and be 2 cm or more long. Liver biopsy is limited by a) sampling error, b) inter-observer variability, and c) the potentially rare complications.[69] There are at least three common systems to evaluate MAFLD biopsies, namely Brunt score,[70] the NAFLD activity score (NAS),[71] and the fatty liver inhibition of progression (FLIP) algorithm and the steatosis, activity, and fibrosis (SAF) scoring system. Emerging evidence suggests that the SAF score provides a more robust histological assessment.[72]

Recommendations:

- Indications for liver biopsy in patients with MAFLD (A1)
  - A typical feature of noninvasive tests is sowing indeterminate or unreliable results.
  - Assessment for dual-etiology liver diseases.
  - Ethically approved research or clinical trials, including during bariatric surgery or cholecystectomy.
- Liver biopsy reporting should be standardized using either the FLIP algorithm and SAF score or the NASH CRN system (B1).

MAFLD-RELATED CIRRHOSIS

The highest risk of hepatic complication is among those with cirrhosis and of nonhepatic complication is among patients with stage 3 fibrosis.[46,73] Classification of cirrhosis depends on prognostic staging—compensated and decompensated cirrhosis[74,75]—based on the presence or absence of clinically evident decompensating events such as jaundice, variceal hemorrhage, ascites, spontaneous bacterial peritonitis, or encephalopathy.

Patients with cirrhosis and past or present evidence of metabolic dysfunction that meet the criteria to diagnose MAFLD with either documentation of MAFLD on a previous liver biopsy or historical documentation of steatosis by hepatic imaging should be considered as having MAFLD-related cirrhosis, even in the absence of hepatic steatosis or typical histology of MAFLD at the time of presentation.[24]

Cirrhosis can be diagnosed by classic findings on ultrasonography, but the diagnosis may be missed when this is obscured by liver fat. In this context, liver stiffness measurement (LSM) can be used to diagnose cirrhosis and provide prognostic information in MAFLD patients in the appropriate clinical context,[76] with mortality rate being higher with increasing LSM.[77] If LSM is not available, fibrosis scores can be used as an initial step to rule out patients who are less likely to have advanced fibrosis or cirrhosis and determine patients who need referral for LSM.[68]

Aside from the prevention and treatment of decompensation events, cirrhosis management should focus on education, lifestyle modification, protecting the liver from further injury (e.g., through vaccination for viral hepatitis and avoidance of hepatotoxic medications), and care coordination;[78] moreover, it remains critical to avoid sarcopenia [Figure 2].

Recommendations

- Patients with cirrhosis in the absence of current steatosis who meet the following criteria should still be considered as having MAFLD-related cirrhosis:
  - Past or present evidence of meeting the criteria to diagnose MAFLD, with at least one of the following:

1) Historical documentation of MAFLD on a previous liver biopsy*.
2) Historical documentation of hepatic steatosis by imaging*. (B2)

**History of past viral hepatitis should be considered as patients may have dual disease etiology.*

DIAGNOSIS AND MONITORING FOR CLINICALLY SIGNIFICANT PORTAL HYPERTENSION AND VARICES

The initial consequence of liver cirrhosis in general, or MAFLD-related cirrhosis in particular, is portal hypertension.[79] The gold-standard for assessment of clinically significant portal hypertension is the direct measurement of HVPG, as this is invasive and not readily available. Alternatively, ultrasound is a feasible and safe technique for detecting morphological abnormalities associated with cirrhosis and an indicative measure of clinically significant portal hypertension. Computed tomography (CT) and MRI are other alternative tools.[80]

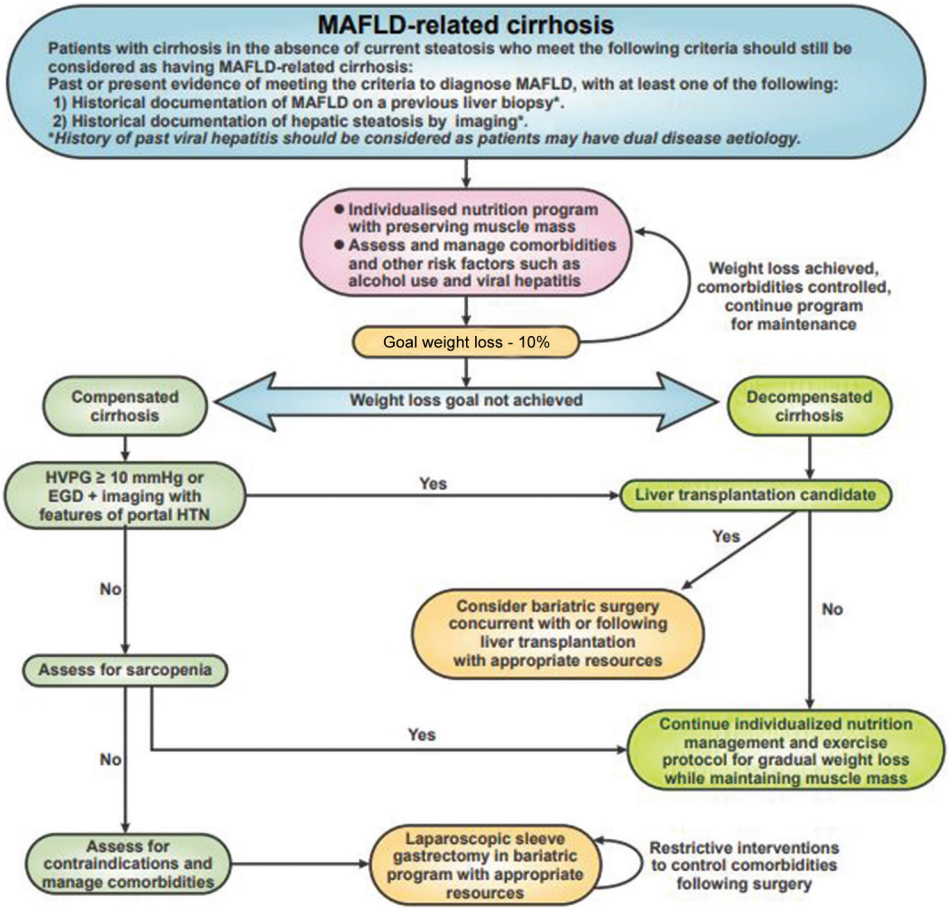

Figure 2: The Egyptian guidelines recommended an algorithm to evaluate and manage patients with MAFLD-related compensated and decompensated cirrhosis.

Patients with MAFLD-related cirrhosis should be screened for gastroesophageal varices according to the Baveno VI criteria, as the prognosis is worse in those with gastroesophageal varices compared to those without.[81,82] The Baveno VI criteria have been recently validated in patients with MAFLD related cirrhosis.[83]

Esophagogastroduodenoscopy (EGD) is required to confirm the existence and size of varices, though it is an invasive procedure with a risk of bleeding.[84] The assessment of LSM is an alternative accepted technique to rule out high-risk varices in patients with compensated cirrhosis. The interpretation of LSM data is as follows: LSM >15 kPa can diagnose cirrhosis, LSM = 10–15 kPa is suggestive of cirrhosis, and LSM <10 kPa in the absence of other clinical signs rules out cirrhosis.[85,86] Patients with LSM >15 kPa should be considered for surveillance for HCC, whereas those with LSM >20–25 kPa and/or thrombocytopenia, the use of EGD may be recommended for confirmation of diagnosis and prophylactic interventions in these patients.[85]

Recommendations

- Screening by EGD for gastroesophageal varices is recommended in patients with MAFLD-associated cirrhosis unless previously diagnosed and treated (B2).
- The exact interval of screening by EGD in patients without gastroesophageal varices is unclear. However, in patients with multiple etiologies and/or those for whom the state of decompensation continues, screening EGD should be repeated every year. For the rest of the patients, screening intervals can be extended up to 2 years (C2).
- Relying on noninvasive tests to diagnose gastroesophageal varices is not recommended due to the low diagnostic accuracy (A1).
- Ultrasound is recommended for detecting cirrhosis. Liver stiffness measurement by transient elastography can be used to exclude high-risk varices in patients with compensated cirrhosis (B2).

SCREENING FOR HCC IN PATIENTS WITH MAFLD

Abdominal ultrasound is the preferred screening tool for HCC due to its availability and cost-effectiveness.[31,87,88] However, it has low sensitivity for detection of early-stage HCC (~47%);[89] therefore, simultaneous measurement of serum biomarker such as AFP is recommended.[89,90] Despite their high diagnostic efficacy, using dynamic imaging such as contrast-enhanced ultrasonography, computed tomography, and MRI for screening for HCC is not recommended as a surveillance modality due to the lack of wide availability and high cost, except for patients in whom the ultrasound quality is suboptimal due to obesity or excessive gas in the alimentary tract or when confirmation is required.[91]

A 6-month screening interval is recommended, which is based on the tumor volume doubling-time of HCC.[92] A randomized controlled trial demonstrated the detection rate of early HCC and prognosis does not differ significantly with 3- or 6-monthly surveillance intervals; 6-monthly surveillance interval has been found to be better than a 12-month interval.[93]

The targeted population for screening are MAFLD patients with cirrhosis. Although noncirrhotic patients with MAFLD are at high risk of HCC,[94] the overall risk in the absence of cirrhosis is relatively low to justify the recommendation of screening in this group of patients, particularly with the very high prevalence of MAFLD.

Recommendations

- Screening for HCC in MAFLD patients with cirrhosis through a combination of abdominal ultrasound and alpha-fetoprotein (AFP) every 6 months is recommended, as it improves overall survival; however, it is not recommended in noncirrhotic patients due to lack of evidence for cost-effectiveness (A1).
- Computed tomography or magnetic resonance imaging may be needed if the ultrasound quality is inadequate (B2).

NONPHARMACOLOGICAL MANAGEMENT OF MAFLD

Lifestyle modifications, including dietary change, weight loss, and exercise intervention, remain the cornerstone therapy and the first-line for this disease.

Diet and Lifestyle Changes

In patients with MAFLD, lifestyle intervention programs and weight loss effectively lead to a reduction in hepatic steatosis, resolution of steatohepatitis, and regression of fibrosis, and improve a patient's quality of life in a dose-dependent manner.

The overall aim of lifestyle intervention should be for gradual weight loss (up to 1 kg/week) with losing 7%–10% of their body weight in obese patients and 5% in nonobese subjects as a primary target. There is no robust evidence to support a particular dietary approach for patients with MAFLD. Generally, a hypocaloric diet (500–1000-kcal deficit), with a daily protein intake of 1.2–1.5 g/kg of body weight/day is recommended. Notably, excess caloric restriction should be avoided as it can exacerbate the risk of sarcopenia, which is a poor predictor outcome in obese cirrhotic patients. Dietary plans should discourage the consumption of fructose and encourage adopting the "Mediterranean type diet"[95] and regular coffee drinking.[96]

In real life, weight loss and more critically sustaining this effect is challenging. Using the 5 A's model (ask, advise, assess, assist, and arrange) may be useful to assess patients' needs and modify their behavior. Increasing clinic visit frequency[97] and/or utilizing an internet-based approach for lifestyle changes[98] have been proposed to maximize the efficacy of weight loss programs in patients with MAFLD.

Recent evidence suggests that alcohol use is associated with hepatic steatosis even in subjects with presumed NAFLD, according to current definitions.[99] In addition, alcohol intake within the limits of the current definition has been reported to increase significantly the risk for progression of fatty liver disease[23,100,101] and increased risk of HCC.[102,103]

Exercise

Regular physical activity and exercise have been demonstrated to have beneficial effects on the entire spectrum of MAFLD, including improvements in hepatic steatosis and health-related quality of life[104] and reduction in liver stiffness, portal hypertension,[105] and risk of HCC.[106]

There is no defined optimal frequency, intensity, duration, and type of physical activity/exercise for the induction of resolution of MAFLD. For the general adult population, physical activity guidelines recommend a total of ≥150 min/week of moderate-intensity exercise or 30 min/day for ≥5 days/week, or vigorous-intensity exercise for ≥75 min/week or ≥20 min/day on ≥3 days/week. Resistance exercise on 2–3 days/week and flexibility exercises >2 days/week are also recommended.[107]

A recent randomized clinical trial demonstrated that both vigorous and moderate exercise and aerobic and resistance exercise reduces hepatic steatosis equally in MAFLD, and the effect appeared to be largely mediated by weight loss.[108,109] Thus, generally, the selection of the type and duration of exercise should be tailored according to patients' preference and the likelihood of compliance. Resistance and moderate exercise may be more feasible than aerobic and vigorous exercise for MAFLD patients with poor fitness. Combined diet/exercise strategies containing a minimum 6 months of high-intensity lifestyle intervention followed by 1 year of a maintenance program are recommended.

Recommendations

- Lifestyle changes, including combined healthy diet and exercise strategies are effective in normalization of liver enzymes levels and improvement of liver histology. (B1)
- Weight loss is beneficial and recommended in patients with MAFLD, regardless of BMI. 7–10% and 5% weight loss is the target in the overweight/obese and nonobese patients with MAFLD, respectively. (B1)
- Physical activity without any pharmacotherapy is enough for MAFLD patients without steatohepatitis or fibrosis (B1)
- There is no particular mandatory dietary approach, and dietary counseling should be individualized. Generally, energy restriction, Mediterranean-type diet, regular coffee drinking, and avoiding processed food and fructose are advisable. (B1)
- Both vigorous and moderate exercise and aerobic exercise and resistance training reduce hepatic steatosis equally in MAFLD, though resistance exercise may be more feasible for patients with poor fitness. Recommendations should be individualized based on patient preferences to enhance long-term adherence. (B2)

BARIATRIC AND METABOLIC THERAPIES (ENDOSCOPIC APPROACHES AND SURGERY) FOR MAFLD

Though not an indication *per se*, MAFLD exists in 65%−90% of all patients who undertake weight loss surgery.[110,111] Multiple retrospective and prospective observational cohort studies from Egypt[112,113] showed consistent results with international findings, with meta-analyses[114-116] suggesting that resolution of hepatic steatosis, steatohepatitis, and fibrosis was observed in >75% of patients.[117]

Special precautions are required when bariatric surgery is considered in patients with MAFLD-related cirrhosis due to the high perioperative risk with a suggested operative mortality of up to 16.3% in those with decompensated disease.[118] Notably, in a recent Egyptian study of 132 cases with Child-A MAFLD-related cirrhosis, laparoscopic sleeve gastrectomy (LSG) was found to be safe and led to improvement of steatosis, steatohepatitis, and fibrosis, after 30-month follow-up.[119]

The utility of endoscopic bariatric and metabolic therapies (EBMT), including intragastric balloons (IGBs) and endoscopic sleeve gastroplasty (ESG), as less invasive and safer interventions compared to the traditional operations are emerging and may represent an attractive option for patients with MAFLD.[120]

Therefore, based on the current evidence, bariatric surgery can be offered to patients with MAFLD only if the following two criteria are met: 1) BMI >40 kg/m^2 or BMI >35 kg/m^2 with obesity-related comorbidities; 2) absence of decompensated cirrhosis or evidence of concomitant portal hypertension. The utility and feasibility of bariatric surgery for patients with MAFLD and BMI ≤35 kg/m^2 is currently unclear, and further studies are required to clarify this aspect.

Recommendations

- Bariatric surgery can be offered to patients with MAFLD only if the following two criteria are met: 1) BMI >40 kg/m^2 or BMI >35 kg/m^2 with obesity-related comorbidities; 2) absence of decompensated cirrhosis or evidence of concomitant portal hypertension. (B1)
- The utility and feasibility of bariatric surgery for patients with MAFLD and BMI ≤35 kg/m^2 is currently unclear. (C2)
- Bariatric (metabolic) surgery improves all MAFLD parameters, including reduction of liver fat, resolution of steatohepatitis, and regression of fibrosis. (B1)
- The decision for offering bariatric (metabolic) surgery for patients with cirrhosis should be individualized because of the high risk of post-operative complications. (C1)

PHARMACOLOGICAL TREATMENT

Due to the shared pathogenic pathways between MAFLD

and T2DM, several anti-diabetic medications have been investigated for the treatment of patients with MAFLD.[121,122] The beneficial effects of pioglitazone on hepatic histology in patients with and without T2DM has been reported in five small-randomized controlled trials.[123-127] However, due to multiple possible concerns with pioglitazone, including weight gain, edema, the development of bladder cancer, and a decrease in bone mineral density, this therapy is not widely used.[128,129] Metformin does not improve hepatic histology in patients with MAFLD.[130-133] However, it improves insulin resistance[130,132,133] and reduces the risk of HCC in these patients, though it should be noted that the studies have not been randomized or prospective.[134,135]

Though some studies have shown that vitamin E can have some role in improving hepatic histology in patients with steatohepatitis,[123,136-138] other studies failed to confirm these findings.[127,132,139,140] A recent study demonstrated that vitamin E decreases the risk of hepatic decompensation, transplant, and death in MAFLD patients with bridging fibrosis or cirrhosis.[141] The development of prostate cancer and hemorrhagic stroke is a possible concern of vitamin E therapy.[142]

Although statins did not show beneficial effects on hepatic histology,[143] they may reduce cardiovascular morbidity in patients with MAFLD.[143,144] Thus, statins can be used safely in patients with MAFLD with hyperlipidemia.

Obeticholic acid (OCA) is a first-in-class selective farnesoid X receptor (FXR) agonist and represents the most advanced drug in development to date; however, it is not approved yet.[145] In terms of adverse events, the main adverse event of OCA was pruritus, which occurred in half of patients that received 25 mg daily. Another major caveat of OCA is the elevation in serum low-density lipid protein (LDL) and decrease in high-density lipid protein (HDL). Thus, statins should be considered in patients with MAFLD with hyperlipidemia or who receive OCA therapy.[145]

There are many pharmacological agents under clinical trials in phase II and phase III development [Table 1] and beyond the scope of discussion in this guideline document.

Recommendations

- Statins reduce cardiovascular morbidity and mortality and can be used in patients who receive obeticholic acid, if needed. (B1)
- Vitamin E may improve histological markers of disease activity; however, there are some concerns about safety. (B2)

Table 1: Pharmacological agents under trials for NAFLD/NASH

Drug	Target	Phase
Obtecholic acid	FXR agonist	III
Aramchol	SCDI inhibitor	III
Lanifibrinor	Pan PAPAR agonist	II
Tropixefor	FXR agonist	LI
Gilofexor (GS 9674)	FXR agonist	II
Elfibrinor	PPAR α/β agonist	II
Saroglitazar	PPAR α/γ agonist	II
Pradigastat	DGAT1 inhibitor	II
TVB 2640	FASN inhibitor	II
Pegbelfermin	FGF 21 analog	II
NGM 282	FG19 analog	II
Belapectin	Galactin 3 inhibitor	II
Simtuzumab	Antibody against LOX 21	II

DGAT1, diacylglycerol acyltransferase 1; FASn, fatty acid synthase; FGF21, fibroblast growth factor 21; FXR, farnesoid X receptor; LOXL2, lysyl oxidase-like 2; liver X receptor; PPAR, peroxisome proliferative activated receptor; SCD1, steroyl-coA desaturase 1.

- Pioglitazone improves histological markers of MAFLD; however, there are some concerns about safety. (B2)
- Metformin has no effect on hepatic histology but improves insulin resistance and may reduce the risk of HCC. (B2)

MONİTORİNG PROGRESS AND RESPONSE TO TREATMENT

Given that the severity of fibrosis is the major determinant of both hepatic-related outcomes and mortality,[146] those with significant fibrosis need the closest monitoring and the following scheme is recommended and can mainly be undertaken at primary care for the stage with no or early fibrosis and using simple noninvasive scores of fibrosis:

Interval of follow-up

1) Patients without fibrosis can be monitored at 2- or 3-year intervals if they do not have concomitant metabolic risk factors or if there has been no worsening of these comorbidities.
2) Patients with fibrosis or evidence uncontrolled concomitant metabolic risk factors should be monitored on an annual basis
3) Patients with cirrhosis should undergo monitoring at 6-month intervals, including surveillance for HCC (please see the next section for details).

Method of follow-up

With acknowledgment of the fact that there is no ideal biomarker of the score with a high predictive value for differentiating different stages of liver fibrosis, we recommend monitoring of fibrosis progression in the clinic by using noninvasive scores (NFS, FIB-4) and ideally if possible in combination with liver stiffness measurement

by transient elastography[147,148] to increase the accuracy of prediction and minimize the gray zone.

Recommendations

- Patients without fibrosis, concomitant metabolic risk factors, or the absence of worsening of metabolic risk factors can be monitored at intervals of 2 or 3 years. (C2)
- Patients with fibrosis or concomitant metabolic risk factors should be monitored on an annual basis by using a combination of noninvasive scores and/or liver stiffness measurement. (C2)
- Patients with cirrhosis should undergo monitoring at 6-month intervals, including surveillance for hepatocellular carcinoma. (A2)

PATIENT REPORTED OUTCOMES IN MAFLD

MAFLD was demonstrated to be associated with low health-related quality of life (HRQoL), independent of other demographics or metabolic comorbidities.[149,150] Instruments for assessing patient reported outcomes (PRO) include questionnaires that evaluate general HRQoL such as Chronic Liver Disease Questionnaire (CLDQ), the Short Form-36 (SF-36), and EuroQoL 5-Dimensions 5-Level (EQ-5D-5L), or disease-specific questionnaires such as NASH-CHECK and CLDQ-NASH.[151-153] Although these questionnaires have been translated into various languages and validated in various countries, these are yet to be well validated in Egypt, and how cultural variation may influence the PROs is not known.

Recommendations:

- Patients with MAFLD seem to have worse HRQoL, physical, fatigue, and mental scores, compared to patients with other causes of chronic liver disease. (B2)
- Integration of patient perspectives on the disease, quality of life, satisfaction, and compliance with lifestyle advice via patient-reported outcomes (PRO) is crucial for developing a holistic patient-centered model of care for MAFLD. (B2)

SPECIAL GROUPS

Lean MAFLD

Although overweight/obesity is classically associated with the development and progression of MAFLD, a recent meta-analysis estimated that within the MAFLD population, 40.8% are non-obese and 19.2% are lean, without differences in the histological severity of disease between lean and obese patients.[154,155] Non-obese patients with MAFLD may have a worse outcome and accelerated disease progression.[156-158] Insulin resistance and altered body fat distribution rather than BMI could be better indicators of MAFLD in such patients and hence the importance of the new diagnostic criteria of MAFLD.[154]

The management of nonobese subjects with MAFLD relies on lifestyle intervention through regular exercise and controlling metabolic comorbidities, irrespective of baseline BMI. A 3%–5% weight reduction may be sufficient in lean MAFLD. In addition, nonobese subjects were found to be more likely to maintain weight reduction and normal liver enzymes in the long term compared to obese subjects.[159]

Recommendations:

- MAFLD can frequently exist in nonobese subjects. (B1)
- Lifestyle intervention with regular exercise is effective in treating MAFLD and in improving overall fitness and metabolic co-morbidities irrespective of baseline BMI. (B1)

Dual Etiologies

As MAFLD is no longer a diagnosis of exclusion and it is now possible to diagnose its coexistence with other liver diseases such as HBV and HCV, meeting the criteria for a diagnosis of MAFLD plus one or more of the other diagnoses as the cause of chronic liver diseases at baseline or at follow-up, should be diagnosed as dual etiology liver disease.

These individuals are likely to have a different natural history and response to therapy than those with liver disease of a "single" etiology.[24] With the high prevalence rates of MAFLD and viral hepatitis in Egypt, it is expected that these disease entities will frequently occur together.

In this regard, a recent study of more than 10,000 consecutive patients with HCV from Egypt estimated that nearly half of these patients have coexisting MAFLD, and this group of patients were at a higher risk of hepatic fibrosis compared to those with HCV.[160]

Recommendations

- Patients with liver diseases such as ALD and viral hepatitis should be carefully evaluated for possible concurrent MAFLD and vice versa (A1).
- Patients with MAFLD should be advised to avoid alcohol or at least to consume the lowest amount possible (B1).
- MAFLD management and that of concomitant diseases should be as per the standard guidelines for each of the diseases (B1).

Cured HCV or Treated HBV Subjects

MAFLD is emerging as a key cause for persistently abnormal liver tests, continuing to drive liver disease progression and offset the beneficial impact of profound virological suppression or sustained virological response and poor outcomes in individuals with chronic HBV and/or HCV infection on end-stage liver disease, HCC burden, and dropout rate from the liver transplant waiting list.[161,162] Treatment of MAFLD in this group should be considered the same as that for noninfected patients. In addition, multiple studies have demonstrated that direct acting antivirals-induced SVR is associated with weight gain, increased serum lipid levels, and hepatic steatosis.[163] Therefore, this group of patients may be more vulnerable to MAFLD-related complications.

Recommendations

- Patients cured of HCV or having profound HBV virological suppression with MAFLD need monitoring because of the increased risk for progression to cirrhosis, development of HCC, as well as extrahepatic-related complications. (B1)
- The exact monitoring schedule is yet to be defined, but these patients can be followed according to the recommendations of MAFLD single etiology. (B2)
- Deterioration of lipid profiles and increase in weight and hepatic steatosis are frequently overlooked post-SVR. Clinicians should actively find, monitor these parameters, and intervene as appropriate, to reduce cardio-cerebral vascular disease risk. (B1)

RAMADAN FASTING

Restriction in meal-consuming timing has emerged as a potential promising dietary approach for the management of obesity and dysmetabolic diseases, including MAFLD. Ramadan fasting has been reported in a study from Egypt on 83 patients with MAFLD to lead to a reduction of the severity of hepatic steatosis and liver enzymes.[164] Another study showed a direct effect of Ramadan fasting on improving noninvasive measures of fibrosis as well as on inflammatory markers and insulin sensitivity.[165] In addition, both preclinical animal studies and human clinical trials have demonstrated that intermittent fasting has wide-spectrum benefits for many health conditions, including MAFLD.[166]

Recommendations

Ramadan fasting is advisable with plethoric beneficial effects in patients with MAFLD (A2).

MANAGEMENT OF MAFLD-RELATED HCC

Metabolic risk factor modification could contribute to the optimum management of patients with MAFLD-related HCC; physical activity has been found to have a positive impact on HCC-related survival.[167] However, as sarcopenia is reported to be a prognostic factor for patients with HCC,[168-175] careful consideration of body composition, including skeletal muscle mass and body fat, is crucial when recommending treating patients with HCC and particularly when recommending physical activity.

T2DM is a risk factor for HCC, and metformin has been demonstrated to significantly reduce the risk of HCC in MAFLD patients with HbA1c levels of >7.0%[134] and extend the survival of HCC patients with T2DM after the curative treatment of HCC.[135] Thus, in MAFLD-related HCC patients with T2DM, metformin with life-style intervention may be recommended. However, further prospective, well-controlled randomized studies including Egyptian patients are required before any strong recommendation can be made.

Recommendations:

- Metformin and lifestyle intervention could be beneficial in MAFLD-related HCC patients, particularly patients with T2DM. (B1)
- Careful consideration of sarcopenia as a prognostic factor and appropriate nutritional therapy is recommended. (C2)

LIVER TRANSPLANTATION FOR MAFLD

MAFLD is emerging as the leading indication for liver transplantation (LT). The related comorbidities with MAFLD directly impact patient evaluation and selection, waitlist morbidity, mortality, and eventually post-transplant

outcomes. Although LT is a radical treatment for cirrhosis, it does not treat these underlying comorbidities; therefore, this population is maintained at an increased risk for CVD and postoperative morbidity after LT.[176] Thus, a careful cardiovascular evaluation is mandatory. Survival after MAFLD-associated liver transplant has been reported to be similar to those for other causes of liver disease.[177] On the contrary, the main causes of mortality in patients with MAFLD following LT are sepsis and cardiovascular disease.[178]

The increasing prevalence of MAFLD in the general population corresponds directly with the increasing prevalence of MAFLD in both the deceased and living donor pools. The use of steatotic livers has been associated with an increased risk of graft failure and/or impaired graft function.[179]

The optimal regime in MAFLD recipients is unclear. Strategies to control associated comorbidities before LT should be prioritized to favorably impact waitlist mortality, decrease the rate of recurrent or *de novo* MAFLD after LT, and improve post-transplant outcome. In addition, immunosuppression including steroids and calcineurins inhibitors can cause or worsen modifiable risk factors and therefore should be minimized. Statins should be encouraged post-LT in those with dyslipidemia and/or pre-existing CVD and may be associated with a survival benefit.[180]

Recommendations

- Liver transplantation should be considered in appropriately selected MAFLD patients with decompensated liver disease or HCC. (B1)
- Patients with MAFLD have a high risk of presence of pre-existing CVD and hence should be thoroughly assessed prior to listing for transplantation and followed up afterwards.. (B1)

CONCLUSION

The burden of MAFLD is rapidly increasing in Egypt and is emerging as a leading cause of chronic liver disease, HCC, and liver transplantation. In addition, it is intimately associated with numerous systemic complications such as T2DM, CVD, CKD, and multiple cancers. In our region, dual etiology, particularly with viral hepatitis, is common and challenging. The Egyptian guideline document for MAFLD is aimed to provide simple and practical recommendations for the assessment and management for the general population along with special populations with MAFLD. Fibrosis is the single major risk factor of all hepatic and extra-hepatic complications of MAFLD, with numerous noninvasive tools for assessment of fibrosis available and increasingly used. Holistic multidisciplinary and patient-centered approaches are needed to provide optimal care for patients with MAFLD. These models should aim to tackle the entire spectrum of the disease that includes not only the resolution of hepatic steatosis and liver injury but also the amelioration of the associated systemic metabolic milieu and control the accompanied comorbidities that aggravate the risk of cardiovascular and other extra-hepatic complications, with patient-reported outcomes being at the core. Lifestyle intervention, including dietary changes and structured exercise, remains the holy grail of management, with an armamentarium of therapeutic options expected to be available over the next few years. In the extreme of the spectrum of the disease, bariatric (metabolic) surgery may be indicated. MAFLD patients with cirrhosis should be considered for surveillance for varices and HCC. Multiple gaps in our knowledge on MAFLD are identified, and a joint effort by various stakeholders for gathering more evidence is the only way forward for the full adoption of these recommendations and tackling this growing burden.

Research priorities and unmet needs in the field

We recommend the following research priorities to improve MAFLD-related health outcomes in Egypt:

- Serum tests and risk stratification algorithms for staging MAFLD and validating the cut-offs of noninvasive scores of fibrosis in the Egyptian MAFLD population.
- Studies to establish and test the efficacy of task shifting and referral pathways based on the MAFLD diagnostic criteria.
- Identifying the characteristics of patients with dual disease (MAFLD and HCV; MAFLD and HBV).
- Characterization of the genetic architecture of MAFLD in this region would be required.
- Studies to compare the diagnostic accuracy, cost-effectiveness, and patient outcomes reported using the NAFLD and MAFLD diagnostic criteria in Egyptian cohorts.
- Relative to their proportion of the global MAFLD population, Egypt is underrepresented in ongoing clinical trials for pharmaceutical treatments. Thus, more clinical trials in Egyptian populations are necessary.

Ethical approval and Informed consent

Nil.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Harbour R, Miller J. A new system for grading recommendations in evidence based guidelines. BMJ 2001;323:334-6.
2. Golzarand M, Mirmiran P, Jessri M, Toolabi K, Mojarrad M, Azizi F. Dietary trends in the Middle East and North Africa: An ecological study (1961 to 2007). Public Health Nutr 2012;15:1835-44.
3. Mahmood A. Nutritional status and anthropometric measurements among women in Egypt, National Survey 2001–2002. Arab J Food Nutr 2004;11:98-107.
4. (WHO). WHO. MENA STEPS. Surveys Final Report. Geneva; 2014.
5. Esmat G, El-Sayed MH, Hassany M, Doss W, Waked I, National Committee for the Control of Viral Hepatitis. One step closer to elimination of hepatitis C in Egypt. Lancet Gastroenterol Hepatol 2018;3:665.
6. Galal OM. The nutrition transition in Egypt: Obesity, undernutrition and the food consumption context. Public Health Nutr 2002;5:141-8.
7. Turk-Adawi K, Sarrafzadegan N, Fadhil I, Taubert K, Sadeghi M, Wenger NK, *et al*. Cardiovascular disease in the Eastern Mediterranean region: Epidemiology and risk factor burden. Nat Rev Cardiol 2018;15:106-19.
8. Azizi F, Hadaegh F, Hosseinpanah F, Mirmiran P, Amouzegar A, Abdi H, *et al*. Metabolic health in the Middle East and north Africa. Lancet Diabetes Endocrinol 2019;7:866-79.
9. Younossi Z, Tacke F, Arrese M, Chander Sharma B, Mostafa I, Bugianesi E, *et al*. Global perspectives on nonalcoholic fatty liver disease and nonalcoholic steatohepatitis. Hepatology 2019;69:2672-82.
10. Guthold R, Stevens GA, Riley LM, Bull FC. Worldwide trends in insufficient physical activity from 2001 to 2016: A pooled analysis of 358 population-based surveys with 1.9 million participants. Lancet Glob Health 2018;6:e1077-86.
11. Ng M, Fleming T, Robinson M, Thomson B, Graetz N, Margono C, *et al*. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980–2013: A systematic analysis for the Global Burden of Disease Study 2013. Lancet 2014;384:766-81.
12. Eslam M, George J. Genetic contributions to NAFLD: Leveraging shared genetics to uncover systems biology. Nat Rev Gastro Hepat 2020;17:40-52.
13. Eslam M, Valenti L, Romeo S. Genetics and epigenetics of NAFLD and NASH: Clinical impact. J Hepatol 2018;68:268-79.
14. Tomah S, EID EM, Abouelmagd MM, Hassan AH, Eldib AH, Hamdy O. 214-LB: Vibration-controlled transient elastography reveals alarming prevalence of nonalcoholic fatty liver disease and fibrosis among young adults in Egypt. Am Diabetes Assoc 2019;68(Supl 1). doi: 10.2337/db19-214-LB.
15. Alkassabany YM, Farghaly AG, El-Ghitany EM. Prevalence, risk factors, and predictors of nonalcoholic fatty liver disease among schoolchildren: A hospital-based study in Alexandria, Egypt. Arab J Gastroenterol 2014;15:76-81.
16. Fouad Y ea. Prevalence of metabolic associated fatty liver disease in an Egyptian Tertiary Care Center. 2021, in press.
17. Abdel Alem S GY, AbdAlla M, Said E, Fouad Y. Capturing patient experience: A qualitative study of change from NAFLD to MAFLD real-time feedback. J Hepatol 2021;74:1261-2.
18. Fouad Y, Gomaa AA, Semida N, Abdel Ghany W, Attia D. Change from NAFLD to MAFLD increases the awareness of fatty liver disease in primary care physicians and specialists. J Hepatol 2021;74:1254-6.
19. Alexander M, Loomis AK, Fairburn-Beech J, van der Lei J, Duarte-Salles T, Prieto-Alhambra D, *et al*. Real-world data reveal a diagnostic gap in non-alcoholic fatty liver disease. BMC Med 2018;16:1-11. doi: 10.1186/s12916-018-1103-x.
20. Standing HC, Jarvis H, Orr J, Exley C, Hudson M, Kaner E, *et al*. GPs' experiences and perceptions of early detection of liver disease: A qualitative study in primary care. Br J Gen Pract 2018;68:e743-9.
21. Bertot LC, Jeffrey GP, Wallace M, MacQuillan G, Garas G, Ching HL, *et al*. Nonalcoholic fatty liver disease-related cirrhosis is commonly unrecognized and associated with hepatocellular carcinoma. Hepatol Commun 2017;1:53-60.
22. Shiha G, Alswat K, Al Khatry M, Sharara AI, Örmeci N, Waked I, *et al*. Nomenclature and definition of metabolic-associated fatty liver disease: A consensus from the Middle East and north Africa. Lancet Gastroenterol Hepatol 2021;6:57-64.
23. Eslam M, Sanyal AJ, George J. Toward more accurate nomenclature for fatty liver diseases. Gastroenterology 2019;157:590-3.
24. Eslam M, Newsome PN, Sarin SK, Anstee QM, Targher G, Romero-Gomez M, *et al*. A new definition for metabolic dysfunction-associated fatty liver disease: An international expert consensus statement. J Hepatol 2020;73:202-9.
25. Eslam M, Alkhouri N, Vajro P, Baumann U, Weiss R, Socha P, *et al*. Defining paediatric metabolic (dysfunction)-associated fatty liver disease: An international expert consensus statement. Lancet Gastroenterol Hepatol 2021;6:864-73.
26. Fouad Y, Elwakil R, Elsahhar M, Said E, Bazeed S, Ali Gomaa A, *et al*. The NAFLD-MAFLD debate: Eminence vs evidence. Liver Int 2021;41:255-60.
27. Yamamura S, Eslam M, Kawaguchi T, Tsutsumi T, Nakano D, Yoshinaga S, *et al*. MAFLD identifies patients with significant hepatic fibrosis better than NAFLD. Liver Int 2020;40:3018-30.
28. Lee H, Lee YH, Kim SU, Chang Kim H. Metabolic dysfunction-associated fatty liver disease and incident cardiovascular disease risk: A nationwide cohort study. Clin Gastroenterol Hepatol 2020;22;19:2138-47.e10.
29. Tsutsumi T, Eslam M, Kawaguchi T, Yamamura S, Kawaguchi A, Nakano D, *et al*. MAFLD better predicts the progression of atherosclerotic cardiovascular risk than NAFLD: Generalized estimating equation approach. Hepatol Res 2021;51:1115-28.
30. Mendez-Sanchez N, Arrese M, Gadano A, Oliveira CP, Fassio E, Arab JP, *et al*. The Latin American Association for the Study of the Liver (ALEH) position statement on the redefinition of fatty liver disease. Lancet Gastroenterol Hepatol 2021;6:65-72.
31. Eslam M, Sarin SK, Wong VW, Fan JG, Kawaguchi T, Ahn SH, *et al*. The Asian Pacific Association for the Study of the Liver clinical practice guidelines for the diagnosis and management of metabolic associated fatty liver disease. Hepatol Int 2020;14:889-919.
32. Zheng KI, Fan JG, Shi JP, Wong VW, Eslam M, George J, *et al*. From NAFLD to MAFLD: A "redefining" moment for fatty liver disease. Chin Med J (Engl) 2020;133:2271-3.
33. Sepanlou SG, Safiri S, Bisignano C, Ikuta KS, Merat S, Saberifiroozi M, *et al*. The global, regional, and national burden of cirrhosis by cause in 195 countries and territories, 1990–2017: A systematic analysis for the Global Burden of Disease Study 2017. Lancet Gastroenterol Hepatol 2020;5:245-66.
34. Dyson J, Jaques B, Chattopadyhay D, Lochan R, Graham J, Das D, *et al*. Hepatocellular cancer: The impact of obesity, type 2 diabetes and a multidisciplinary team. J Hepatol 2014;60:110-7.
35. Sharafi H, Alavian SM. The rising threat of hepatocellular carcinoma in the Middle East and North Africa region: Results from global burden of disease study 2017. Clin Liver Dis (Hoboken) 2019;14:219-23.
36. Fouad Y GA, Kamal E, Bazeed S, Said E, Gaber Y. Temporal trends of primary liver cancer caused by specific aetiologies in the Egyptian Population. 2021, in press.
37. Younossi ZM, Otgonsuren M, Henry L, Venkatesan C, Mishra A,

Erario M, *et al*. Association of nonalcoholic fatty liver disease (NAFLD) with hepatocellular carcinoma (HCC) in the United States from 2004 to 2009. Hepatology 2015;62:1723-30.
38. Stine JG, Wentworth BJ, Zimmet A, Rinella ME, Loomba R, Caldwell SH, *et al*. Systematic review with meta-analysis: Risk of hepatocellular carcinoma in non-alcoholic steatohepatitis without cirrhosis compared to other liver diseases. Aliment Pharmacol Ther 2018;48:696-703.
39. Eshraghian A, Taghavi Seyed A, Nikeghbalian S, Kazemi K, Shamsaeefar A, Mansourian M, *et al*. Nonalcoholic steatohepatitis is the most rapidly growing indication for liver transplantation in Iranian patients. Iran J Gastroenterol Hepatol (Govaresh) 2017;22. doi: 10.6002/ect. 2019.0205.
40. Hasan F, Daher HB. The burden and clinical care pathways of nonalcoholic steatohepatitis in the Middle east. Clin Liver Dis (Hoboken) 2019;14:207-11.
41. Tariq R, Axley P, Singal AK. Extra-hepatic manifestations of nonalcoholic fatty liver disease: A review. J Clin Exp Hepatol 2020;10:81-7.
42. Musso G, Gambino R, Tabibian JH, Ekstedt M, Kechagias S, Hamaguchi M, *et al*. Association of non-alcoholic fatty liver disease with chronic kidney disease: A systematic review and meta-analysis. Plos Med 2014;11:e1001680.
43. Targher G, Bertolini L, Rodella S, Lippi G, Zoppini G, Chonchol M. Relationship between kidney function and liver histology in subjects with nonalcoholic steatohepatitis. Clin J Am Soc Nephrol 2010;5:2166-71.
44. Ong JP, Pitts A, Younossi ZM. Increased overall mortality and liver-related mortality in non-alcoholic fatty liver disease. J Hepatol 2008;49:608-12.
45. Angulo P, Kleiner DE, Dam-Larsen S, Adams LA, Bjornsson ES, Charatcharoenwitthaya P, *et al*. Liver fibrosis, but no other histologic features, is associated with long-term outcomes of patients with nonalcoholic fatty liver disease. Gastroenterology 2015;149:389-97. e10.
46. Vilar-Gomez E, Calzadilla-Bertot L, Wai-Sun Wong V, Castellanos M, Aller-de la Fuente R, Metwally M, *et al*. Fibrosis severity as a determinant of cause-specific mortality in patients with advanced nonalcoholic fatty liver disease: A multi-national cohort study. Gastroenterology 2018;155:443-57.e17.
47. Francque SM, van der Graaff D, Kwanten WJ. Non-alcoholic fatty liver disease and cardiovascular risk: Pathophysiological mechanisms and implications. J Hepatol 2016;65:425-43.
48. Wong VW, Adams LA, de Ledinghen V, Wong GL, Sookoian S. Noninvasive biomarkers in NAFLD and NASH-current progress and future promise. Nat Rev Gastroenterol Hepatol 2018;15:461-78.
49. Hernaez R, Lazo M, Bonekamp S, Kamel I, Brancati FL, Guallar E, *et al*. Diagnostic accuracy and reliability of ultrasonography for the detection of fatty liver: A meta-analysis. Hepatology 2011;54:1082-90.
50. Karlas T, Petroff D, Sasso M, Fan JG, Mi YQ, de Lédinghen V, *et al*. Individual patient data meta-analysis of controlled attenuation parameter (CAP) technology for assessing steatosis. J Hepatol 2017;66:1022-30.
51. Caussy C, Alquiraish MH, Nguyen P, Hernandez C, Cepin S, Fortney LE, *et al*. Optimal threshold of controlled attenuation parameter with MRI-PDFF as the gold standard for the detection of hepatic steatosis. Hepatology 2018;67:1348-59.
52. Wong VW, Petta S, Hiriart JB, Cammà C, Wong GL, Marra F, *et al*. Validity criteria for the diagnosis of fatty liver by M probe-based controlled attenuation parameter. J Hepatol 2017;67:577-84.
53. Caussy C, Brissot J, Singh S, Bassirian S, Hernandez C, Bettencourt R, *et al*. Prospective, same-day, direct comparison of controlled attenuation parameter with the M vs the XL probe in patients with nonalcoholic fatty liver disease, using magnetic resonance imaging–proton density fat fraction as the standard. Clin Gastroenterol Hepatol 2020;18:1842-50. e6.
54. Caussy C, Reeder SB, Sirlin CB, Loomba R. Noninvasive, quantitative assessment of liver fat by MRI-PDFF as an endpoint in NASH trials. Hepatology 2018;68:763-72.
55. Bedogni G, Bellentani S, Miglioli L, Masutti F, Passalacqua M, Castiglione A, *et al*. The fatty liver index: A simple and accurate predictor of hepatic steatosis in the general population. BMC gastroenterology 2006;6:33. doi: 10.1186/1471-230X-6-33.
56. Xu Z, Li H, Tian S, Wu J, Li X, Liu ZL, *et al*. Blood biomarkers for the diagnosis of hepatic steatosis in metabolic dysfunction-associated fatty liver disease. J Hepatol 2020;73:1264-5.
57. Wai C-T, Greenson JK, Fontana RJ, Kalbfleisch JD, Marrero JA, Conjeevaram HS, *et al*. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. Hepatology 2003;38:518-26.
58. Sterling RK, Lissen E, Clumeck N, Sola R, Correa MC, Montaner J, *et al*. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. Hepatology 2006;43:1317-25.
59. Angulo P, Hui JM, Marchesini G, Bugianesi E, George J, Farrell GC, *et al*. The NAFLD fibrosis score: A noninvasive system that identifies liver fibrosis in patients with NAFLD. Hepatology 2007;45:846-54.
60. Kaya E, Bakir A, Eren F, Yilmaz Y. The utility of noninvasive scores in non-alcoholic fatty liver disease patients with normal and elevated serum transaminases. Hepatol Forum2020;1:8.
61. Alkayyali T, Qutranji L, Kaya E, Bakir A, Yilmaz Y. Clinical utility of noninvasive scores in assessing advanced hepatic fibrosis in patients with type 2 diabetes mellitus: A study in biopsy-proven non-alcoholic fatty liver disease. Acta Diabetol 2020;57:613-618.
62. Daniels SJ, Leeming DJ, Eslam M, Hashem AM, Nielsen MJ, Krag A, *et al*. ADAPT: An algorithm incorporating PRO-C3 accurately identifies patients with NAFLD and advanced fibrosis. Hepatology 2019;69:1075-86.
63. Eslam M, Wong GL-H, Hashem AM, Chan HL, Nielsen MJ, Leeming DJ, *et al*. A sequential algorithm combining ADAPT and liver stiffness can stage metabolic-associated fatty liver disease in hospital-based and primary care patients. Am J Gastroenterol 2020;116:984-93.
64. Lee HW, Wong GL, Kwok R, Choi KC, Chan CK, Shu SS, *et al*. Serial transient elastography examinations to monitor patients with type 2 diabetes: A prospective cohort study. Hepatology 2020;72:1230-41.
65. Shiha GE, El-Etreby S, Bahgat M, Hamed M, El Sherbini M, Ghoneem EA, *et al*. Chronic hepatitis C patients with obesity: Do we need two operators for accurate evaluation of liver stiffness? Ann Hepatol 2018;17:795-801.
66. Imajo K, Kessoku T, Honda Y, Tomeno W, Ogawa Y, Mawatari H, *et al*. Magnetic resonance imaging more accurately classifies steatosis and fibrosis in patients with nonalcoholic fatty liver disease than transient elastography. Gastroenterology 2016;150:626-37.e7.
67. Park CC, Nguyen P, Hernandez C, Bettencourt R, Ramirez K, Fortney L, *et al*. Magnetic resonance elastography vs transient elastography in detection of fibrosis and noninvasive measurement of steatosis in patients with biopsy-proven nonalcoholic fatty liver disease. Gastroenterology 2017;152:598-607 e2.
68. Chan WK, Treeprasertsuk S, Goh GB, Fan JG, Song MJ, Charatcharoenwitthaya P, *et al*. Optimizing use of nonalcoholic fatty liver disease fibrosis score, fibrosis-4 score, and liver stiffness measurement to identify patients with advanced fibrosis. Clin Gastroenterol Hepatol 2019;17:2570-80.e37.
69. Spinzi G, Terruzzi V, Minoli G. Liver biopsy. N Engl J Med 2001;344:2030.
70. Brunt EM, Janney CG, Di Bisceglie AM, Neuschwander-Tetri BA, Bacon BR. Nonalcoholic steatohepatitis: A proposal for grading and staging the histological lesions. Am J Gastroenterol 1999;94:2467-74.
71. Kleiner DE, Brunt EM, Van Natta M, Behling C, Contos MJ, Cummings OW, *et al*. Design and validation of a histological scoring system for nonalcoholic fatty liver disease. Hepatology

2005;41:1313-21.
72. Bedossa P, Poitou C, Veyrie N, Bouillot JL, Basdevant A, Paradis V, *et al*. Histopathological algorithm and scoring system for evaluation of liver lesions in morbidly obese patients. Hepatology 2012;56:1751-9.
73. Dulai PS, Singh S, Patel J, Soni M, Prokop LJ, Younossi Z, *et al*. Increased risk of mortality by fibrosis stage in nonalcoholic fatty liver disease: Systematic review and meta-analysis. Hepatology 2017;65:1557-65.
74. D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: A systematic review of 118 studies. J Hepatol 2006;44:217-31.
75. Scaglione S, Kliethermes S, Cao G, Shoham D, Durazo R, Luke A, *et al*. The epidemiology of cirrhosis in the United States: A population-based study. J Clin Gastroenterol 2015;49:690-6.
76. Wong VW, Vergniol J, Wong GL, Foucher J, Chan HL, Le Bail B, *et al*. Diagnosis of fibrosis and cirrhosis using liver stiffness measurement in nonalcoholic fatty liver disease. Hepatology 2010;51:454-62.
77. Boursier J, Vergniol J, Guillet A, Hiriart JB, Lannes A, Le Bail B, *et al*. Diagnostic accuracy and prognostic significance of blood fibrosis tests and liver stiffness measurement by FibroScan in non-alcoholic fatty liver disease. J Hepatol 2016;65:570-8.
78. Ge PS, Runyon BA. Treatment of patients with cirrhosis. New Engl J Med 2016;375:767-77.
79. Chalasani N, Wilson L, Kleiner DE, Cummings OW, Brunt EM, Unalp A, *et al*. Relationship of steatosis grade and zonal location to histological features of steatohepatitis in adult patients with non-alcoholic fatty liver disease. J Hepatol 2008;48:829-34.
80. Berzigotti A, Merkel C, Magalotti D, Tiani C, Gaiani S, Sacerdoti D, *et al*. New abdominal collaterals at ultrasound: A clue of progression of portal hypertension. Dig Liver Dis 2008;40:62-7.
81. Augustin S, Pons M, Maurice JB, Bureau C, Stefanescu H, Ney M, *et al*. Expanding the Baveno VI criteria for the screening of varices in patients with compensated advanced chronic liver disease. Hepatology 2017;66:1980-8.
82. Stafylidou M, Paschos P, Katsoula A, Malandris K, Ioakim K, Bekiari E, *et al*. Performance of Baveno VI and expanded Baveno VI criteria for excluding high-risk varices in patients with chronic liver diseases: A systematic review and meta-analysis. Clin Gastroenterol Hepatol 2019;17:1744-55.e11.
83. Zheng KI, Liu C, Li J, Zhao L, Zheng MH, Wang F, *et al*. Validation of Baveno VI and expanded Baveno VI criteria to identify high-risk varices in patients with MAFLD-related compensated cirrhosis. J Hepatol 2020;73:1571-3.
84. Garcia-Tsao G, Abraldes JG, Berzigotti A, Bosch J. Portal hypertensive bleeding in cirrhosis: Risk stratification, diagnosis, and management: 2016 practice guidance by the American Association for the study of liver diseases. Hepatology (Baltimore, Md) 2017;65:310-35.
85. de Franchis R, Baveno VIF. Expanding consensus in portal hypertension: Report of the Baveno VI Consensus Workshop: Stratifying risk and individualizing care for portal hypertension. J Hepatol 2015;63:743-52.
86. Eslam M, Ampuero J, Jover M, Abd-Elhalim H, Rincon D, Shatat M, *et al*. Predicting portal hypertension and variceal bleeding using non-invasive measurements of metabolic variables. Ann Hepatol 2013;12:420-30.
87. Loomba R, Lim JK, Patton H, El-Serag HB. AGA clinical practice update on screening and surveillance for hepatocellular carcinoma in patients with nonalcoholic fatty liver disease: Expert review. Gastroenterology 2020;158:1822-30.
88. Singal AG, Lampertico P, Nahon P. Epidemiology and surveillance for hepatocellular carcinoma: New trends. J Hepatol 2020;72:250-61.
89. Tzartzeva K, Obi J, Rich NE, Parikh ND, Marrero JA, Yopp A, *et al*. Surveillance imaging and alpha fetoprotein for early detection of hepatocellular carcinoma in patients with cirrhosis: A meta-analysis. Gastroenterology 2018;154:1706-18.e1.
90. Mikami S, Tateishi R, Hagiwara S, Sato M, Minami T, Uchino K, *et al*. Tumor markers are more useful in patients undergoing surveillance for hepatocellular carcinoma with unreliable results by ultrasonography. Hepatol Res 2015;45:415-22.
91. Park HJ, Jang HY, Kim SY, Lee SJ, Won HJ, Byun JH, *et al*. Non-enhanced magnetic resonance imaging as a surveillance tool for hepatocellular carcinoma: Comparison with ultrasound. J Hepatol 2020;72:718-24.
92. Barbara L, Benzi G, Gaiani S, Fusconi F, Zironi G, Siringo S, *et al*. Natural history of small untreated hepatocellular carcinoma in cirrhosis: A multivariate analysis of prognostic factors of tumor growth rate and patient survival. Hepatology 1992;16:132-7.
93. Santi V, Trevisani F, Gramenzi A, Grignaschi A, Mirici-Cappa F, Del Poggio P, *et al*. Semiannual surveillance is superior to annual surveillance for the detection of early hepatocellular carcinoma and patient survival. J Hepatol 2010;53:291-7.
94. Mittal S, El-Serag HB, Sada YH, Kanwal F, Duan Z, Temple S, *et al*. Hepatocellular carcinoma in the absence of cirrhosis in United States veterans is associated with nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol 2016;14:124-31.e1.
95. Estruch R, Ros E, Salas-Salvadó J, Covas MI, Corella D, Arós F, *et al*. Primary prevention of cardiovascular disease with a Mediterranean diet. New Engl J Med 2013;368:1279-90.
96. Wijarnpreecha K, Thongprayoon C, Ungprasert P. Coffee consumption and risk of nonalcoholic fatty liver disease: A systematic review and meta-analysis. Eur J Gastroen Hepatol 2017;29:e8-12.
97. Dudekula A, Rachakonda V, Shaik B, Behari J. Weight loss in nonalcoholic fatty liver disease patients in an ambulatory care setting is largely unsuccessful but correlates with frequency of clinic visits. Plos One 2014;9;9:e111808. doi: 10.1371/journal.pone. 0111808.
98. Mazzotti A, Caletti MT, Brodosi L, Di Domizio S, Forchielli ML, Petta S, *et al*. An internet-based approach for lifestyle changes in patients with NAFLD: Two-year effects on weight loss and surrogate markers. J Hepatol 2018;69:1155-63.
99. Long MT, Massaro JM, Hoffmann U, Benjamin EJ, Naimi TS. Alcohol use is associated with hepatic steatosis among persons with presumed non-alcoholic fatty liver disease. Clin Gastroenterol Hepatol 2020;18:1831-41.e5.
100. Chang Y, Cho YK, Kim Y, Sung E, Ahn J, Jung HS, *et al*. Nonheavy drinking and worsening of noninvasive fibrosis markers in nonalcoholic fatty liver disease: A cohort study. Hepatology 2019;69:64-75.
101. Blomdahl J, Nasr P, Ekstedt M, Kechagias S. Moderate alcohol consumption is associated with advanced fibrosis in non-alcoholic fatty liver disease and shows a synergistic effect with type 2 diabetes mellitus. Metabolism 2021;115:154439.
102. Aberg F, Helenius-Hietala J, Puukka P, Farkkila M, Jula A. Interaction between alcohol consumption and metabolic syndrome in predicting severe liver disease in the general population. Hepatology 2018;67:2141-9.
103. Ascha MS, Hanouneh IA, Lopez R, Tamimi TAR, Feldstein AF, Zein NN. The incidence and risk factors of hepatocellular carcinoma in patients with nonalcoholic steatohepatitis. Hepatology 2010;51:1972-8.
104. Abdelbasset WK, Tantawy SA, Kamel DM, Alqahtani BA, Soliman GS. A randomized controlled trial on the effectiveness of 8-week high-intensity interval exercise on intrahepatic triglycerides, visceral lipids, and health-related quality of life in diabetic obese patients with nonalcoholic fatty liver disease. Medicine 2019;98:e14918.
105. Oh S, So R, Shida T, Matsuo T, Kim B, Akiyama K, *et al*. High-intensity aerobic exercise improves both hepatic fat content and stiffness in sedentary obese men with nonalcoholic fatty liver disease. Sci Rep-Uk 2017;7:43029. doi: 10.1038/srep43029.
106. Saran U, Humar B, Kolly P, Dufour J-F. Hepatocellular carcinoma and lifestyles. J Hepatol 2016;64:203-14.
107. Garber CE, Blissmer B, Deschenes MR, Franklin BA, Lamonte MJ, Lee IM, *et al*. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: Guidance for prescribing exercise. Med

Sci Sports Exerc 2011;43:1334-59.
108. Zhang H-J, He J, Pan L-L, Ma ZM, Han CK, Chen CS, *et al*. Effects of moderate and vigorous exercise on nonalcoholic fatty liver disease: A randomized clinical trial. JAMA Intern Med 2016;176:1074-82.
109. Abdelbasset WK, Tantawy SA, Kamel DM, Alqahtani BA, Elnegamy TE, Soliman GS, *et al*. Effects of high-intensity interval and moderate-intensity continuous aerobic exercise on diabetic obese patients with nonalcoholic fatty liver disease: A comparative randomized controlled trial. Medicine 2020;99:e19471. doi: 10.1097/MD.0000000000019471.
110. Seki Y, Kakizaki S, Horiguchi N, Hashizume H, Tojima H, Yamazaki Y, *et al*. Prevalence of nonalcoholic steatohepatitis in Japanese patients with morbid obesity undergoing bariatric surgery. J Gastroenterol 2016;51:281-9.
111. Subichin M, Clanton J, Makuszewski M, Bohon A, Zografakis JG, Dan A. Liver disease in the morbidly obese: A review of 1000 consecutive patients undergoing weight loss surgery. Surg Obes Relat Dis 2015;11:137-41.
112. Salman MA, Salman AA, Omar HS, Abdelsalam A, Mostafa MS, Tourky M, *et al*. Long-term effects of one-anastomosis gastric bypass on liver histopathology in NAFLD cases: A prospective study. Surg Endosc 2020;35:1889-941.
113. Salman AA, Sultan AA, Abdallah A, Abdelsalam A, Mikhail HM, Tourky M, *et al*. Effect of weight loss induced by laparoscopic sleeve gastrectomy on liver histology and serum adipokine levels. J Gastroen Hepatol 2020;35:1769-73.
114. Aguilar-Olivos NE, Almeda-Valdes P, Aguilar-Salinas CA, Uribe M, Mendez-Sanchez N. The role of bariatric surgery in the management of nonalcoholic fatty liver disease and metabolic syndrome. Metabolism 2016;65:1196-207.
115. Clanton J, Subichin M. The Effects of Metabolic Surgery on fatty liver disease and nonalcoholic steatohepatitis. Surg Clin North Am 2016;96:703-15.
116. Hafeez S, Ahmed MH. Bariatric surgery as potential treatment for nonalcoholic fatty liver disease: A future treatment by choice or by chance? J Obes 2013;2013. doi: 10.1155/2013/83927.
117. Lassailly G, Caiazzo R, Ntandja-Wandji L-C, Gnemmi V, Baud G, Verkindt H, *et al*. Bariatric surgery provides long-term resolution of nonalcoholic steatohepatitis and regression of fibrosis. Gastroenterology 2020;159:1290-301.
118. Mosko JD, Nguyen GC. Increased perioperative mortality following bariatric surgery among patients with cirrhosis. Clin Gastroenterol Hepatol 2011;9:897-901.
119. Salman MA, Mikhail HM, Nafea MA, Sultan AA, Elshafey HE, Tourky M, *et al*. Impact of laparoscopic sleeve gastrectomy on fibrosis stage in patients with child-A NASH-related cirrhosis. Surg Endosc 2020;35:1269-77.
120. Salomone F, Sharaiha RZ, Boškoski I. Endoscopic bariatric and metabolic therapies for non-alcoholic fatty liver disease: Evidence and perspectives. Liver Int 2020;40:1262-8.
121. Chalasani N, Younossi Z, Lavine JE, Charlton M, Cusi K, Rinella M, *et al*. The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. Hepatology 2018;67:328-57.
122. European Association for the Study of the Liver, European Association for the Study of Diabetes, European Association for the Study of Obesity. EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. J Hepatol 2016;64:1388-402.
123. Sanyal AJ, Chalasani N, Kowdley KV, McCullough A, Diehl AM, Bass NM, *et al*. Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis. New Engl J Med 2010;362:1675-85.
124. Cusi K, Orsak B, Bril F, Lomonaco R, Hecht J, Ortiz-Lopez C, *et al*. Long-term pioglitazone treatment for patients with nonalcoholic steatohepatitis and prediabetes or type 2 diabetes mellitus: A randomized trial. Ann Intern Med 2016;165:305-15.
125. Belfort R, Harrison SA, Brown K, Darland C, Finch J, Hardies J, *et al*. A placebo-controlled trial of pioglitazone in subjects with nonalcoholic steatohepatitis. New Engl J Med 2006;355:2297-307.
126. Aithal GP, Thomas JA, Kaye PV, Lawson A, Ryder SD, Spendlove I, *et al*. Randomized, placebo-controlled trial of pioglitazone in nondiabetic subjects with nonalcoholic steatohepatitis. Gastroenterology 2008;135:1176-84.
127. Bril F, Biernacki DM, Kalavalapalli S, Lomonaco R, Subbarayan SK, Lai J, *et al*. Role of vitamin E for nonalcoholic steatohepatitis in patients with type 2 diabetes: A randomized controlled trial. Diabetes Care 2019;42:1481-8.
128. Mehtala J, Khanfir H, Bennett D, Ye Y, Korhonen P, Hoti F. Pioglitazone use and risk of bladder cancer: A systematic literature review and meta-analysis of observational studies. Diabetol Int 2019;10:24-36.
129. Portillo-Sanchez P, Bril F, Lomonaco R, Barb D, Orsak B, Bruder JM, *et al*. Effect of pioglitazone on bone mineral density in patients with nonalcoholic steatohepatitis: A 36-month clinical trial. J Diabetes 2019;11:223-31.
130. Haukeland JW, Konopski Z, Eggesbo HB, von Volkmann HL, Raschpichler G, Bjøro K, *et al*. Metformin in patients with non-alcoholic fatty liver disease: A randomized, controlled trial. Scand J Gastroenterol 2009;44:853-60.
131. Musso G, Gambino R, Cassader M, Pagano G. A meta-analysis of randomized trials for the treatment of nonalcoholic fatty liver disease. Hepatology 2010;52:79-104.
132. Lavine JE, Schwimmer JB, Van Natta ML, Molleston JP, Murray KF, Rosenthal P, *et al*. Effect of vitamin E or metformin for treatment of nonalcoholic fatty liver disease in children and adolescents: The TONIC randomized controlled trial. JAMA 2011;305:1659-68.
133. Li Y, Liu L, Wang B, Wang J, Chen D. Metformin in non-alcoholic fatty liver disease: A systematic review and meta-analysis. Biomed Rep 2013;1:57-64.
134. Vilar-Gomez E, Calzadilla-Bertot L, Wai-Sun Wong V, Castellanos M, Aller-de la Fuente R, Eslam M, *et al*. Type 2 diabetes and metformin use associate with outcomes of patients with non-alcoholic steatohepatitis-related, Child-Pugh A cirrhosis. Clin Gastroenterol Hepatol 2021;19:136-45.e6.
135. Zhou J, Ke Y, Lei X, Wu T, Li Y, Bao T, *et al*. Meta-analysis: The efficacy of metformin and other anti-hyperglycemic agents in prolonging the survival of hepatocellular carcinoma patients with type 2 diabetes. Ann Hepatol 2020;19:320-8.
136. Harrison SA, Torgerson S, Hayashi P, Ward J, Schenker S. Vitamin E and vitamin C treatment improves fibrosis in patients with nonalcoholic steatohepatitis. Am J Gastroenterol 2003;98:2485-90.
137. Hoofnagle JH, Van Natta ML, Kleiner DE, Clark JM, Kowdley KV, Loomba R, *et al*. Vitamin E and changes in serum alanine aminotransferase levels in patients with non-alcoholic steatohepatitis. Aliment Pharmacol Ther 2013;38:134-43.
138. Sato K, Gosho M, Yamamoto T, Kobayashi Y, Ishii N, Ohashi T, *et al*. Vitamin E has a beneficial effect on nonalcoholic fatty liver disease: A meta-analysis of randomized controlled trials. Nutrition 2015;31:923-30.
139. Sarkhy AA, Al-Hussaini AA, Nobili V. Does vitamin E improve the outcomes of pediatric nonalcoholic fatty liver disease? A systematic review and meta-analysis. Saudi J Gastroenterol 2014;20:143-53.
140. Amanullah I, Khan YH, Anwar I, Gulzar A, Mallhi TH, Raja AA. Effect of vitamin E in non-alcoholic fatty liver disease: A systematic review and meta-analysis of randomised controlled trials. Postgrad Med J 2019;95:601-11.
141. Vilar-Gomez E, Vuppalanchi R, Gawrieh S, Ghabril M, Saxena R, Cummings OW, *et al*. Vitamin E improves transplant-free survival and hepatic decompensation among patients with nonalcoholic steatohepatitis and advanced fibrosis. Hepatology 2020;71:495-509.
142. Klein EA, Thompson IM, Jr., Tangen CM, Crowley JJ, Lucia MS, Goodman PJ, *et al*. Vitamin E and the risk of prostate cancer: The selenium and vitamin E cancer prevention trial (SELECT). JAMA 2011;306:1549-56.
143. Eslami L, Merat S, Malekzadeh R, Nasseri-Moghaddam S, Aramin H.

Statins for non-alcoholic fatty liver disease and non-alcoholic steatohepatitis. Cochrane Database Syst Rev 2013:CD008623. doi: 10.1002/14651858.CD008623.pub2.
144. Athyros VG, Tziomalos K, Gossios TD, Griva T, Anagnostis P, Kargiotis K, *et al*. Safety and efficacy of long-term statin treatment for cardiovascular events in patients with coronary heart disease and abnormal liver tests in the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) Study: A post-hoc analysis. Lancet 2010;376:1916-22.
145. Eslam M, Alvani R, Shiha G. Obeticholic acid: Towards first approval for NASH. Lancet 2019;394:2131-3.
146. Taylor RS, Taylor RJ, Bayliss S, Hagström H, Nasr P, Schattenberg JM, *et al*. Association between fibrosis stage and outcomes of patients with non-alcoholic fatty liver disease: A systematic review and meta-analysis. Gastroenterology 2020;158:1611-25.e12.
147. Kaya E, Bakir A, Kani HT, Demirtas CO, Keklikkiran C, Yilmaz Y. Simple noninvasive scores are clinically useful to exclude, not predict, advanced fibrosis: A study in Turkish patients with biopsy-proven nonalcoholic fatty liver disease. Gut Liver 2019;14:486-91.
148. Jafarov F, Kaya E, Bakir A, Eren F, Yilmaz Y. The diagnostic utility of fibrosis-4 or nonalcoholic fatty liver disease fibrosis score combined with liver stiffness measurement by fibroscan in assessment of advanced liver fibrosis: A biopsy-proven nonalcoholic fatty liver disease study. Eur J Gastroen Hepat 2020;32:642-9.
149. Younossi ZM, Stepanova M, Anstee QM, Lawitz EJ, Wai-Sun Wong V, Romero-Gomez M, *et al*. Reduced patient-reported outcome scores associate with level of fibrosis in patients with nonalcoholic steatohepatitis. Clin Gastroenterol Hepatol 2019;17:2552-60.e10.
150. Huber Y, Boyle M, Hallsworth K, Tiniakos D, Straub BK, Labenz C, *et al*. Health-related quality of life in nonalcoholic fatty liver disease associates with hepatic inflammation. Clin Gastroenterol Hepatol 2019;17:2085-92 e1.
151. Younossi ZM. Patient-reported outcomes and the economic effects of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis: The value proposition. Hepatology 2018;68:2405-12.
152. Doward L, Balp MM, Twiss J, Slota C, Cryer D, Langford A, *et al*. Measuring what matters to patients: The development of the NASH-CHECK, a new patient-reported outcome instrument for nonalcoholic steatohepatitis. J Hepatol 2018;68:S570.
153. Younossi ZM, Stepanova M, Henry L, Racila A, Lam B, Pham HT, *et al*. A disease-specific quality of life instrument for non-alcoholic fatty liver disease and non-alcoholic steatohepatitis: CLDQ-NAFLD. Liver Int 2017;37:1209-18.
154. Eslam M, Fan J-G, Mendez-Sanchez N. Non-alcoholic fatty liver disease in non-obese individuals: The impact of metabolic health. Lancet Gastroenterol Hepatol 2020;5:713-5.
155. Ye Q, Zou B, Yeo YH, Li J, Huang DQ, Wu Y, *et al*. Global prevalence, incidence, and outcomes of non-obese or lean non-alcoholic fatty liver disease: A systematic review and meta-analysis. Lancet Gastroenterol Hepatol 2020;5:739-52.
156. Dela Cruz AC, Bugianesi E, George J, Day CP, Liaquat H, Charatcharoenwitthaya P, *et al*. Characteristics and long-term prognosis of lean patients with nonalcoholic fatty liver disease. Gastroenterology 2014;146:S909.
157. Chen F, Esmaili S, Rogers G, Bugianesi E, Petta S, Marchesini G, *et al*. Lean NAFLD: A distinct entity shaped by differential metabolic adaptation. Hepatology 2020;71:1213-27.
158. Eslam M, Chen F, George J. NAFLD in Lean Asians. Clin Liver Dis (Hoboken) 2021;16:240-3.
159. Wong VW-S, Wong GL-H, Chan RS-M, Shu SS, Cheung BH, Li LS, *et al*. Beneficial effects of lifestyle intervention in non-obese patients with non-alcoholic fatty liver disease. J Hepatol 2018;69:1349-56.
160. Attia D FY, Abdel Razik W, El-Akel W, Eslam M, Waked I. Metabolic associated fatty liver disease in the chronic hepatitis C patients. 2021, inpress.
161. Noureddin M, Wong MM, Todo T, Lu SC, Sanyal AJ, Mena EA. Fatty liver in hepatitis C patients post-sustained virological response with direct-acting antivirals. World J Gastroenterol 2018;24:1269-77.
162. Peleg N, Issachar A, Arbib OS, Cohen-Naftaly M, Braun M, Leshno M, *et al*. Liver steatosis is a strong predictor of mortality and cancer in chronic hepatitis B regardless of viral load. JHEP Rep 2019;1:9-16.
163. Fouad Y, Lazarus JV, Negro F, Peck-Radosavljevic M, Sarin SK, Ferenci P, *et al*. MAFLD considerations as a part of the global hepatitis C elimination effort: An international perspective. Aliment Pharmacol Ther 2021;53:1080-9.
164. Ebrahimi S, Gargari BP, Aliasghari F, Asjodi F, Izadi A. Ramadan fasting improves liver function and total cholesterol in patients with nonalcoholic fatty liver disease. Int J Vitam Nutr Res 2020;90:95-102.
165. Mari A, Khoury T, Baker M, Baker A, Mahamid M. The impact of Ramadan fasting on fatty liver disease severity: A retrospective case control study from Israel. Isr Med Assoc J 2021;23:94-8.
166. de Cabo R, Mattson MP. Effects of intermittent fasting on health, aging, and disease. New Engl J Med 2019;381:2541-51.
167. Hashida R, Kawaguchi T, Koya S, Hirota K, Goshima N, Yoshiyama T, *et al*. Impact of cancer rehabilitation on the prognosis of patients with hepatocellular carcinoma. Oncol Lett 2020;19:2355-67.
168. Harimoto N, Shirabe K, Yamashita YI, Ikegami T, Yoshizumi T, Soejima Y, *et al*. Sarcopenia as a predictor of prognosis in patients following hepatectomy for hepatocellular carcinoma. Br J Surg 2013;100:1523-30.
169. Fujiwara N, Nakagawa H, Kudo Y, Tateishi R, Taguri M, Watadani T, *et al*. Sarcopenia, intramuscular fat deposition, and visceral adiposity independently predict the outcomes of hepatocellular carcinoma. J Hepatol 2015;63:131-40.
170. Harimoto N, Yoshizumi T, Shimokawa M, Sakata K, Kimura K, Itoh S, *et al*. Sarcopenia is a poor prognostic factor following hepatic resection in patients aged 70 years and older with hepatocellular carcinoma. Hepatol Res 2016;46:1247-55.
171. Nishikawa H, Nishijima N, Enomoto H, Sakamoto A, Nasu A, Komekado H, *et al*. Prognostic significance of sarcopenia in patients with hepatocellular carcinoma undergoing sorafenib therapy. Oncol Lett 2017;14:1637-47.
172. Ha Y, Kim D, Han S, Chon YE, Lee YB, Kim MN, *et al*. Sarcopenia predicts prognosis in patients with newly diagnosed hepatocellular carcinoma, independent of tumor stage and liver function. Cancer Res Treat 2018;50:843-51.
173. Imai K, Takai K, Watanabe S, Hanai T, Suetsugu A, Shiraki M, *et al*. Sarcopenia impairs prognosis of patients with hepatocellular carcinoma: The role of liver functional reserve and tumor-related factors in loss of skeletal muscle volume. Nutrients 2017;9:1054. doi: 10.3390/nu9101054.
174. Takada H, Kurosaki M, Nakanishi H, Takahashi Y, Itakura J, Tsuchiya K, *et al*. Impact of pre-sarcopenia in sorafenib treatment for advanced hepatocellular carcinoma. PLoS One 2018;13:e0198812.
175. Mardian Y, Yano Y, Ratnasari N, Choridah L, Wasityastuti W, Setyawan NH, *et al*. Sarcopenia and intramuscular fat deposition are associated with poor survival in Indonesian patients with hepatocellular carcinoma: A retrospective study. BMC Gastroenterol 2019;19:229.
176. Yalamanchili K, Saadeh S, Klintmalm GB, Jennings LW, Davis GL. Nonalcoholic fatty liver disease after liver transplantation for cryptogenic cirrhosis or nonalcoholic fatty liver disease. Liver Transpl 2010;16:431-9.
177. Wang X, Li J, Riaz D, Shi G, Liu C, Dai Y. Outcomes of liver transplantation for nonalcoholic steatohepatitis: A systematic review and meta-analysis. Clin Gastroenterol Hepatol 2014;12:394-402.e1.
178. Neal DA, Tom BD, Luan JA, Wareham NJ, Gimson AE, Delriviere LD, *et al*. Is there disparity between risk and incidence of cardiovascular disease after liver transplant? Transplantation 2004;77:93-9.
179. McCormack L, Dutkowski P, El-Badry AM, Clavien P-A. Liver transplantation using fatty livers: Always feasible? J Hepatol 2011;54:1055-62.
180. Patel SS, Rodriguez VA, Siddiqui MB, Faridnia M, Lin FP, Chandrakumaran A, *et al*. The impact of coronary artery disease and statins on survival after liver transplantation. Liver Transpl 2019;25:1514-23.